REMARKS

The Amendment, filed in response to the Office Action mailed April 2, 2010, is believed to fully address all issues raised in the Office Action. Reconsideration on the merits and allowance of the application are respectfully requested.

Disposition of Claims and Claim Amendment

Claims 1-13 are all the claims pending in the application. Claims 11-13 are withdrawn from consideration. Claims 1-10 have been considered and rejected.

In the instant application, claim 1 is amended.

Amended claim 1, which recites "crystallized," may be supported, for example, by [0062]-[0066] of the published application of the instant application. Also, Applicants note that the Examiner recognizes that the specification supports for preparing crystallized form of the drug. Page 14, lines 2-3 from the bottom, of the Office Action.

Summary of Rejections

In the Office Action, claims 1-9 are maintained rejected under 35 U.S.C. 103(a) as being unpatentable over Patel et al. (US Pre-Grant Publication 2003/0064097) in combination with Kawamura et al. (US PreGrant Publication 2004/0219208).

In the Office Action, claim 10 is maintained rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Patel and Kawamura as set forth above with respect to claim 1 in combination with Nielsen et al. (USPN 5,716,558).

In rejecting claims 1-10, the Examiner asserts that Patel teaches methods for preparing multiparticulate compositions using processes which comprise applying an encapsulation coat onto a substrate (e.g. spray coating and nanoencapsulation) as well as collection of the ensuing particles [0223]. According to the Office, preparation of the encapsulation coating solution is taught as solubilizing or suspending a composition in a mixture comprising an organic solvent and a supercritical fluid, and which can further comprise additives and paragraph [0257] of Patel specifically teaches that multiple organic solvents may be combined as the organic solvent of the coating solutions.

The Office recognizes that Patel does not expressly teach removal (e.g. displacement) of the mixed organic solvent portion of the dispersing medium by washing the coated particles with additional supercritical fluid, nor does Patel expressly teaches Applicants' instantly claimed polymer/active weight ratio, percent range of the hydrophilic polymer or the weight ratio of the two organic solvents mixed.

The Office resorts Kawamura as teaching a process for preparing a sustained-release preparation comprising injectable microcapsules or microspheres [0225] and [0226] which comprises an AII antagonist and an anticancer drug (Abstract; claim 1).

It is the Office's position that it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a nano-scale paclitaxel solid dispersion (e.g. suspension) by contacting a paclitaxel/additive/mixed alcohol solvent solution with a supercritical fluid, displacing said alcohol solvent with supercritical fluid and recover the resulting particles, as taught and suggested by the combined teachings of Patel and Kawamura.

With respect to claim 10, the Office states that neither Patel nor Kawamura teach the temperature or pressure application parameters for the supercritical fluid as set forth by

Applicants in claim 10. Nielsen is relied upon as teaching methods for spraying liquid compositions by using compressed fluids such as carbon dioxide, to form solid particulates and coating powders which may be produced with narrow particle size distributions (Abstract); and further teaching that compressed carbon dioxide fluid may be sprayed at a temperature of 60°C and a pressure of 1600 pounds/sq. inch (1 bar/14.5 psi) or about 110.3 bar (col. 13, lines 19-26).

The Office asserts that it would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to have sprayed a supercritical fluid (e.g. carbon dioxide) using Applicants' instantly claimed physical parameters in view of Nielsen's teaching that application of a supercritical fluid to a liquid water-borne polymeric composition comprising a mixed organic solvent produced a dry, collectable powder (Example 9).

Applicant respectfully traverses for the following reasons.

The combined teachings of Patel, Kawamura, and Nielsen fail to teach all and every limitations of independent claim.

The combined teachings of Patel, Kawamura, and Nielsen fail to the recitation "spraying the *solution mixture of Step 1) to a supercritical fluid to form crystallized particles* of the mixture of paclitaxel and the pharmaceutically acceptable additive, the crystallized particles containing *paclitaxel of an altered crystallinity*."

No guidance or motivation to choose and combine paclitaxel and supercritical fluid process and change the crystallinity of paclitaxel.

In addition, the subject invention improves the solubility of, especially, paclitaxel, by using a supercritical fluid, thereby changing the crystallinity of paclitaxel. That is, the feature of the subject invention resides in the unique combination of a drug and a process for forming a solid dispersion thereof.

However, according to Patel, paclitaxel is one of a boilerplate list of pharmaceutically active ingredients, and there is no embodiment confirming an improved solubility of a composition comprising paclitaxel; and Kawamura only teaches that removal of water and organic solvent using supercritical fluid.

Nielsen is related to a method for spraying liquid compositions containing volatile solvent by using compressed fluids, such as carbon dioxide or ethane, to form solid particulates, coating powders, and catalyst materials. The solid particulates can be produced with narrow particle size distributions. Nielsen reports that drier water-borne coatings can be applied to substrates by using compressed fluids to spray water-borne coating compositions having conventional water levels, thereby reducing runs and sags and shortening dry times.

Further, none of the cited references, Patel, Kawamura, and Nielsen, discloses any relationship between solubility and crystallinity of a drug changed by using a supercritical fluid.

Thus, Patel, Kawamura, and Nielsen fail to disclose or suggest that, when using supercritical fluid method among numerous methods for preparing a solid dispersion, the solubility of paclitaxel among such a large number of drugs can be remarkably improved by the change of crystallinity of paclitaxel.

Nielsen merely reports the reduction of the dry time of the catalyst composition powder by using compressed fluid such as carbon dioxide.

Accordingly, even if the cited references are combined together, a person skilled in the art would not have been able to select paclitaxel and supercritical fluid method and conceive the unique process for the improvement of paclitaxel solid dispersion of the subject invention.

Claimed invention shows unexpectedly remarkable effects

Moreover, the effects stemming from the unique combination of paclitaxel and a supercritical fluid are recognized as unexpectedly remarkable compared with those of the cited reference. Specifically, the solubilities of paclitaxel solid dispersions prepared by the supercritical fluid process of the subject invention are remarkably higher (about 3,000 times) than that of the solid dispersion prepared by using liquid carbon dioxide or a conventional paclitaxel powder (see Table 25 of the subject specification). In contrast, although the compositions are not for paclitaxel, the dissolution ratios of the glyburide composition in Example 2 and the progestetone composition in Example 3 of Patel show merely 2 and 3 times higher than that of the pure bulk drug (see Figures 1, 2A and 2B of Patel). Furthermore, the amounts of surfactants (e.g., Myrj 52) comprised in the composition for further improving solubility of the subject invention, i.e., 2.5 to 25g, is much lower than those employed in Examples 2 to 5, and 13 to 28 of Patel.

The Examiner asserts that the unexpected results are compared only with Patel, but not other references. In response, Applicant respectfully submits that the unexpected results may be compared with with the closest prior art to be effective to rebut a *prima facie* case of obviousness. *In re Burckel*, 592 F.2d 1175, 201 USPQ 67 (CCPA 1979).

Accordingly, the subject invention defined in claims 1 to 10 reciting claim 1 is evidently patentable and unobvious over the cited references. Withdrawal of the rejections is respectfully requested.

Response to Claim Rejection under 35 USC § 112

In the Office Action, claim 1 and dependent claims 2-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. In particular, the recitations "recrystallization" and "recrystallized" of claims 1 and 10 are rejected. The Examiner asserts that the "recrystallization" means a repetitive crystallization process (cited Merriam-Webster dictionary) and the instant application specification at best supports a method for preparing an initial crystallized form of the drug, but not a re-crystallized form.

In response, without conceding the Examiner's interpretation of "recrystallization," solely in order to advance the prosecution, Applicants amend the term "recrystallization" to "crystallization." The limitation "2) spraying the solution mixture of Step 1) to a supercritical fluid to form crystallized particles of the mixture of paclitaxel and the pharmaceutically acceptable additive, the crystallized particles containing paclitaxel of an altered crystallinity" in claim 1 and the term "crystallized" are supported by, at least, the disclosure of paragraphs [0063]. Therefore, the currently amended claims 1 and 10 comply with the written description requirement and withdrawal of the section 112, first paragraph rejection.

In addition, Applicants respectfully submit that the term "recrystallization" in chemical art is understood as "a process for procedure for purifying compounds," rather than a process which performs repeatative crystallization. The most typical situation is that a desired "compound A" is contaminated by a small amount of "impurity B. It includes varous technology such as single-sovlent recrystallization, multi-sovlent recrystallization, hot filtration-recrystallization.

http://en.wikipedia.org/wiki/Recrystallization_(chemistry), visited on July 1, 2010. A copy of the cited webpage is attached.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number **202-775-7588**.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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Attachment: A copy of http://en.wikipedia.org/wiki/Recrystallization_(chemistry), visited on July 1, 010